Effect of Obstructive Sleep Apnea on Frequency of Stroke in Patients With Atrial Fibrillation

Dmitry M. Yaranov, MD[a,*], Athanasios Smyrlis, MD[b], Natalia Usatii, MD[a], Amber Butler, BS[c], Joann R. Petrini, PhD, MPH[c], Jose Mendez, MD[d], and Mark K. Warshofsky, MD[b]

Obstructive sleep apnea (OSA) is an independent risk factor for ischemic stroke that is not included in the usual cardioembolic risk assessments for patients with atrial fibrillation (AF). The aim of this study was to investigate the impact of OSA on stroke rate in patients with AF. Patients with AF and new diagnoses of OSA were identified from retrospective chart review. Those with histories of stroke at the time of the sleep study were excluded. The primary outcome was the incidence of stroke, determined by a physician investigator blinded to the results of polysomnography. Subgroup analysis was performed among different $CHADS_2$ and CHA_2DS_2-VASc scores. Of 5,138 patients screened for OSA, 402 (7.7%) had AF and 332 (6.4%) met the inclusion criteria. Among the study population, the occurrence of first-time stroke was 22.9%. Ischemic stroke was more common in patients with OSA compared with patients without (25.4% vs 8.2% respectively, $p = 0.006$). After controlling for age, male gender, and coronary artery disease, the association between OSA and stroke remained statistically significant, with an adjusted odds ratio of 3.65 (95% confidence interval 1.252 to 10.623). A positive dose effect of the apnea-hypopnea index on the rate of stroke was observed ($p = 0.0045$). Subgroup analysis showed significantly higher rates of stroke in patients with $CHADS_2$ scores of 0 and CHA_2DS_2-VASc scores of 0 and 1 and co-morbid OSA. In conclusion, OSA in patients with AF is an independent predictor of stroke. This association may have important clinical implications in ischemic stroke risk stratification. **(Am J Cardiol 2015;115:461−465)**

Atrial fibrillation (AF) is an independent risk factor for stroke.[1] Approximately 25% of patients with AF has documented obstructive sleep apnea (OSA).[2] Multiple studies indicate a strong association between ischemic stroke and OSA.[3−6] The role OSA plays with regard to stroke in patients with AF has not been well delineated.[7] Risk assessment tools are used to estimate the risk for stroke and the need for antithrombotic therapy for patients with AF. This traditionally has been accomplished by the application of the $CHADS_2$ risk score. Modifications of this scoring system have resulted in the CHA_2DS_2-VASc score, which is currently the only assessment tool recommended in the 2014 American Heart Association, American College of Cardiology, and Heart Rhythm Society guideline for the management of patients with AF.[8] Because these traditional cardioembolic risk stratification systems do not account for OSA as a risk factor, we sought to study stroke risk in patients with AF while accounting for the presence of OSA. The primary aim of this study was to evaluate the stroke risk attributed to OSA in patients with AF.

Methods

We conducted a retrospective cohort study of patients referred to the Western Connecticut Health Network Department of Pulmonary, Critical Care, and Sleep Medicine for polysomnography from January 1, 2008, to December 31, 2011. The study sample was limited to patients ≥18 years of age who underwent their first overnight polysomnographic studies. Of all patients who underwent sleep studies, those with previous diagnoses of AF were identified. The exposure group consisted of subjects with apnea-hypopnea index (AHI) values ≥5 and higher; patients with AHI values <5 constituted the comparison group. The follow-up period was defined as the time from index sleep study to the chart review and on average was 4.4 years.

Patients were excluded if they had histories of ischemic stroke or transient ischemic attack at the time of the sleep study. Those patients who underwent split studies without diagnostic polysomnography were eliminated from the study sample. Patients with diagnoses of central sleep apnea were also excluded from the study.

Data collected from the time of polysomnography included age, gender, body mass index, and smoking status. In addition, stroke risk-factor data including diabetes mellitus, congestive heart failure, hypertension, and hyperlipidemia were collected. $CHADS_2$ and CHA_2DS_2-VASc scores were calculated for each patient at the time of polysomnography. Data regarding prophylactic anticoagulation was also collected. For those patients who met the primary end point, anticoagulation status was recorded as the status before the event. The physician investigator blinded to the

Departments of [a]Medicine, [b]Cardiology, [c]Research and Medical Education, and [d]Pulmonary, Critical Care, and Sleep Medicine, Danbury Hospital, Western Connecticut Health Network, Danbury, Connecticut. Manuscript received October 6, 2014; revised manuscript received and accepted November 17, 2014.

See page 464 for disclosure information.

*Corresponding author: Tel: (917) 547-9995; fax: (203) 739-4912.
E-mail address: dmitry.yaranov@wchn.org (D.M. Yaranov).

0002-9149/14/$ - see front matter
http://dx.doi.org/10.1016/j.amjcard.2014.11.027

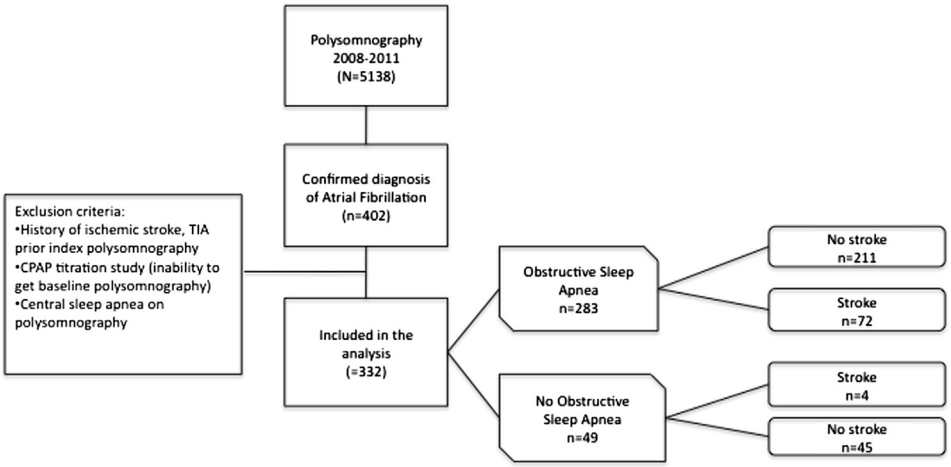

Figure 1. Design of the study.

Table 1
Demographic and clinical characteristics of the patients at baseline*

Variable	Obstructive Sleep Apnea		P value
	No (N=49)	Yes (N=283)	
Age (years)	67.10 (±12.1)	69.06 (±12.1)	0.29
Body-mass index (kg/m^2)	32.26 (±8.0)	33.2 (±7.2)	0.41
Men	29 (59.2%)	207 (73.1%)	0.04
Hypertension	31 (63.3%)	188 (66.4%)	0.74
Hyperlipidemia	37 (76%)	220(78%)	0.81
Diabetes mellitus	17 (34.7%)	89 (31.4%)	0.74
Congestive heart failure	10 (20.4%)	76 (26.9%)	0.38
Coronary artery disease (History of myocardial infarction, angina, percutaneous coronary intervention, or coronary artery bypass graft surgery)	10 (20.4%)	100 (35.3%)	0.04
Apnea hypopnea index	2.60 (±1.4)	36.18 (±29.3)	-
Percent of time spent with O2 saturation <90%	-	22.17 (±27.0)	-
Minimal oxygen saturation during polysomnography	-	79.27 (±9.6)	-
$CHADS_2$ score	1.45 ± 1.2	1.6 ±1.1	0.73
CHA_2DS_2-VASc score	2.65 ± 1.6	2.87 ±1.9	0.88

* Plus − minus values are means ± SD.

OSA status of the patient assessed prevalence of first-time ischemic stroke by reviewing electronic medical records. Diagnosis was determined according to criteria of the National Institute of Neurological Disorders and Stroke for the classification of cerebrovascular events.[9] The diagnosis of stroke had to have been established by a neurologist. The primary outcome was the incidence of ischemic stroke or transient ischemic attack.

Continuous positive airway pressure (CPAP) use and compliance data were obtained from the outpatient chart review. Patients were deemed compliant if they used CPAP for >4 hours per night, ≥70% of the nights in a 30-day period (data obtained from data cards or wireless transmission). Patients were evaluated in the pulmonary and sleep department for 3 consecutive visits after CPAP setup.

The diagnosis of coronary artery disease was made if the medical record noted a history of myocardial infarction, angina, or coronary angiography revealing the presence of disease, percutaneous coronary intervention, or coronary artery bypass graft surgery.

Heart failure was assigned if the medical record documented the presence of the entity or if any cardiac imaging revealed a left ventricular ejection fraction <50%. Diabetes mellitus was recorded if the medical record had noted the presence of type I or II diabetes mellitus or the use of hypoglycemic medications. Hypertension and hyperlipidemia were recorded if diagnoses were noted in medical records.

The diagnosis of AF was determined through review of electronic medical records, including all hospital admissions, outpatient electrocardiograms, discharge and consult notes, Holter monitor reports, and hospital telemonitor strips.

All polysomnographic studies were conducted at the Western Connecticut Health Network sleep laboratory, and all patients were evaluated by a board-certified sleep physician. The diagnosis of OSA was defined as an AHI ≥5. OSA status was further classified as mild (AHI 5 to 15), moderate (AHI >15 to 30), or severe (AHI >30), in accordance with the American Academy of Sleep Medicine criteria.[10] This study was approved by the Western Connecticut Health Network Institutional Review Board.

Table 2
Univariate analysis

Variable	Odds ratio	Confidence interval	P value
Obstructive Sleep Apnea	3.839	1.33-11.05	0.008
Body-mass index >30	1.01	1.93-3.47	0.93
Smoking	0.975	0.59-1.63	0.92
Hypertension	1.354	0.77-2.36	0.33
Hyperlipidemia	0.75	0.32-1.75	0.5
Coronary artery disease	1.33	1.79-2.27	0.05
Diabetes mellitus	1.03	1.33-2.28	0.06
Congestive heart failure	1.33	1.33-2.34	0.37
Age >75	2.45	2.45-4.16	0.001

Table 3
Odds ratio of stroke across $CHADS_2$ groups by obstructive sleep apnea status

$CHADS_2$ score (number of patients)	Odds ratio	95 % confidence interval
0 (n=63)	2.0	1.22 − 18.09
1 (n=96)	1.29	1.15 − 1.44
2 (n=102)	1.9	0.39 − 9.38
3 (n=61)	3.77	0.51 − 27.60
4 (=10)	1.6	0.93 − 2.74

Table 4
Odds ratio of stroke across CHA_2DS_2VASc groups by obstructive sleep apnea status

CHA_2DS_2VASc score (number of patients)	Odds ratio	95% Confidence interval
0 (n=29)	1.62	1.15 - 2.26
1 (n=52)	1.32	0.14 − 12.51
2 (n=61)	1.26	1.09 − 1.44
3 (n=69)	1.76	0.34 − 9.10
4 (n=60)	1.46	1.22 − 1.75
5 (n=48)	2.65	0.30 − 24.14
6 (n=13)	1.20	0.07 − 3.04

Baseline characteristics are presented as means and standard deviations. An analysis of variance was used to compare mean values. Categorical data were compared with the use of chi-square tests. Multiple logistic regression analysis was performed with covariates that were statistically significantly associated with the outcome on univariate analysis. Statistical significance was set at $p < 0.05$. Subgroup analysis of patients on the basis of their $CHADS_2$ and CHA_2DS_2-VASc scores was performed. For every subgroup, univariate analysis was performed with stroke as the dependent variable and OSA as the covariate. Odds ratios were regarded as significant if the 95% confidence interval (CI) did not cross 1, corresponding to a p value <0.05.

All statistical analysis was performed using JMP version 9.0 (SAS Institute Inc., Cary, North Carolina).

Results

Of 5,138 patients who underwent sleep studies for any reason at the Western Connecticut Health Network sleep laboratory during the study period, 402 (7.7%) had previous AF and were eligible for inclusion in the study (Figure 1). After applying the exclusion criteria, 332 patients (6.4%) were included in the study.

OSA was identified in 283 patients (85.2%). The percentage of men was higher among patients with OSA compared with those without (73.1% and 59.2%, respectively, $p = 0.047$), as was the percentage of patients with coronary artery disease (35.3% vs 20.4%, respectively, $p = 0.048$). No other recorded clinical characteristics differed between the 2 groups. Mean $CHADS_2$ score did not differ significantly between groups (1.45 ± 1.24 among non-OSA patients and 1.6 ± 1.06 among patients with OSA), nor did mean CHA_2DS_2-VASc score (2.65 ± 1.62 among non-OSA patients and 2.87 ± 1.91 among patients with OSA). All demographic and relevant clinical characteristics are listed in Table 1.

The occurrence of first-time stroke in the study population was 22.9%. The prevalence of stroke was more common in patients with OSA compared with non-OSA patients (25.4% and 8.2%, respectively, $p = 0.006$). The odds ratio for first-time stroke in AF patients with OSA compared with those without OSA was 3.84 (95% CI 1.334 to 11.047). On multiple logistic regression analysis, the association between OSA and stroke remained statistically significant after controlling for parameters that were significantly associated with outcome on univariate analysis (Table 2), with an adjusted odds ratio of 3.65 (95% CI 1.252 to 10.623).

A dose effect relation was observed between AHI and the incidence of stroke ($p = 0.0045$). Additionally, an incremental increase in the incidence of stroke in OSA patients was observed across all $CHADS_2$ and CHA_2DS_2-VASc groups. Subgroup analysis was performed after stratification of OSA and non-OSA groups on the basis of $CHADS_2$ and CHA_2DS_2-VASc scores. Among patients with $CHADS_2$ scores of 0 and 1, significantly increased incidence of stroke was detected in patients with OSA compared with those without (Table 3). Among patients with CHA_2DS_2-VASc scores of 0, the odds ratio of having a stroke in patients with OSA was 1.62 (95% CI 1.155 to 2.259) (Table 4).

We were able to determine the status of compliance with CPAP in 252 patients (89%) with OSA. Patients who were not compliant with CPAP were more likely to have had strokes than those who were compliant (18.5% vs 10.3%, $p = 0.004$). After controlling for age, gender, and CAD, the association remained statistically significant, and the adjusted odds ratio was 1.75 (95% CI 1.16 to 2.60).

Anticoagulation profile review of the study population revealed that patients with $CHADS_2$ and CHA_2DS_2-VASc scores of 0 were not receiving anticoagulation at any point of the study.

Discussion

This is the first study to provide evidence that OSA is an independent risk factor for stroke in a population of patients with AF. Our results demonstrate that OSA is associated with an increased incidence of stroke, and this association remains significant after accounting for other cardiovascular risk factors.

Several prospective cohort studies have identified OSA as an independent risk factor for stroke after accounting for potential confounding risk factors.[11−15] However, most of these studies examined populations that had only a certain percentage of patients with AF, and the primary aim of those studies was to investigate the relation between OSA and stroke in the general population.[16] A recent study did find higher rates of AF in patients with OSA with first-time stroke, but that study examined the association in a population with OSA,[17] whereas in our study, we examined the role of OSA in stroke risk in the context of an AF population. We were able to demonstrate that AF patients with OSA are 3.6 times more likely to have a first-time stroke than those without. This finding was independent of age, gender, body mass index, diabetes mellitus, hypertension, and coronary artery disease.

The mechanism by which OSA plays a role in the pathogenesis of stroke in patients with AF can be speculated upon. OSA is thought to promote hypertension, changes in cerebral tissue oxygenation and vascular autoregulation, as well as generalized atherosclerosis and dyslipidemia via hypoxia and inflammatory cytokines.[18−21] The upper airway collapse with persisting respiratory efforts and abrupt changes in intrathoracic pressure may lead to left atrial enlargement, providing an environment more conducive to thrombus formation in the setting of AF.[22] Up to 80% of patients with OSA are undiagnosed.[23,24] Evaluating all patients with polysomnography seems to be the only definitive way to determine OSA status. The high rates of OSA in patients with AF and our study findings demonstrate the importance of screening in this patient population.

The severity of OSA has been shown to be associated with an increased all-cause mortality in younger and older populations.[13,25] In our study population, we were able to show a statistically significant dose response of AHI on the incidence of stroke in patients with AF. The preponderance of our data strongly suggests that in patients with AF, OSA increases the risk for stroke, thus increasing morbidity and potentially mortality.

A lower rate of stroke in OSA patients compliant with CPAP reinforces the role of untreated sleep apnea in patients with AF. Response to treatment in this group of patients needs to be further assessed in a prospective study, as CPAP may be used as a treatment modality. There are several ongoing trials evaluating CPAP use and cardiovascular event rates, and they will potentially be able to answer this question.[26]

The Framingham study defined AF as a risk factor for stroke,[1] and the $CHADS_2$ and CHA_2DS_2-VASc scores were developed and validated later to aid in the decision to prophylactically anticoagulate patients to decrease the risk for stroke.[27] However, these 2 risk-scoring systems were developed before OSA was recognized as an independent risk for stroke. There is ongoing debate with regard to OSA's being added to the cardioembolic risk assessment in patients with AF.[16] Our study contributes to this discussion, and the results suggest that the presence of OSA should be considered in the cardioembolic risk assessment in these patients.

All patients in this study were stratified on the basis of their $CHADS_2$ and CHA_2DS_2-VASc scores, and subgroup analysis revealed higher statistically significant rates of strokes in patients with low risk and co-morbid OSA. Those patients with $CHADS_2$ and CHA_2DS_2-VASc scores of 0 were not receiving anticoagulation, yet in this supposedly low-risk group, those with OSA had a significantly increased risk for stroke if OSA was present. In contrast, the presence of OSA does not increase rates of stroke in patients with higher scores. The lack of a dose response in those groups can be attributed to appropriate anticoagulation in this high-risk population. The inclusion of OSA in stroke risk stratification scores may change current clinical practice regarding what were previously thought to be very low risk patients. Validation of this concept with large prospective studies will be beneficial in determining the role that the presence of OSA plays in cardioembolic risk tools in patients with AF.

The retrospective design of this study is a limitation. However, by excluding all patients who had histories of stroke at the time of the index sleep study, we attempted to mitigate any selection bias among the groups. The relatively stringent exclusion criteria limited our sample size, but nonetheless we were able to show a statistically significant difference between those with and without OSA. Because our study population was derived from all patients referred to the sleep laboratory, OSA prevalence was high in our study, which may have introduced bias. The nature of our study precluded the ability to determine the actual burden of AF, and it is possible that our population was not a homogenous one with regard to chronic versus paroxysmal AF. However, several trials have shown no difference between risk for stroke in patients with paroxysmal and chronic AF.[28−30]

Disclosures

The authors have no conflicts of interest to disclose.

1. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham study. *Stroke* 1991;22:983−988.
2. Holmqvist F, Guan N, Zhu Z, Kowey P, Allen L, Fonarow G, Hylek E, Mahaffey K, Chang P, Holmes D, Peterson E, Piccini J, Gersh BJ. Obstructive sleep apnea and atrial fibrillation: findings from ORBIT-AF. *J Am Coll Cardiol* 2014;63:A292.
3. Hart RG, Halperin JL. Atrial fibrillation and stroke: concepts and controversies. *Stroke* 2001;32:803−808.
4. Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP. Pathophysiology of sleep apnea. *Physiol Rev* 2010;90:47−112.
5. Gami AS, Pressman G, Caples SM, Kanagala R, Gard JJ, Davison DE, Malouf JF, Ammash NM, Friedman PA, Somers VK. Association of atrial fibrillation and obstructive sleep apnea. *Circulation* 2004;110:364−367.
6. Mehra R, Benjamin EJ, Shahar E, Gottleib DJ, Nawabit R, Kirchner HL, Sahadevan J, Redline S; Sleep Heart Health Study. Association of nocturnal arrhythmias with sleep disordered breathing: the sleep heart health study. *Am J Respir Crit Care Med* 2006;173:910−916.
7. Mansukhani MP, Bellolio MF, Kolla BP, Enduri S, Somers VK, Stead LG. Worse outcome after stroke in patients with obstructive sleep apnea: an observational cohort study. *J Stroke Cerebrovasc Dis* 2011;20:401−405.
8. January CT, Wann LS, Alpert JS, Calkins H, Cleveland JC Jr, Ciqarroa JE, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2014;64:e1−e76.

9. Whisnant JD, Busford JR, Bernstein EF, Cooper ES, Dyken MI, Eastone D. National Institute of Neurological Disorders and Stroke special report: classification of cerebrovascular disease. *Stroke* 1990;21:637−676.
10. Epstein LJ, Kristo D, Strollo PJ, Friedman N, Malhotra A, Patil SP, Ramar K, Rogers R, Schwab RJ, Weaver EM, Weinstein MD. Adult Obstructive Sleep Apnea Task Force of the American Academy of Sleep Medicine. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. *J Clin Sleep Med* 2009;5:263−276.
11. Redline S, Yenokyan G, Gottlieb DJ, Shahar E, O'Connor TG, Resnick HE, Diener-West M, Sanders MH, Wolf PA, Geraghty EM, Ali T, Lebowitz M, Punjabi NM. Obstructive sleep apnea-hypopnea and incident stroke: the Sleep Heart Health Study. *Am J Respir Crit Care Med* 2010;182:269−277.
12. Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet* 2005;365:1046−1053.
13. Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V. Obstructive sleep apnea as a risk factor for stroke and death. *N Engl J Med* 2005;353:2034−2041.
14. Munoz R, Duran-Cantolla J, Martinez-Vila E, Gallego J, Rubio R, Aizpuru F, De La Torre G. Severe sleep apnea and risk of ischemic stroke in the elderly. *Stroke* 2006;37:2317−2321.
15. Valham F, Mooe T, Rabben T, Stenlund H, Wiklund U, Franklin KA. Increased risk of stroke in patients with coronary artery disease and sleep apnea: a 10-year follow-up. *Circulation* 2008;11:955−960.
16. Yazdan-Ashoori P, Baranchuk A. Obstructive sleep apnea may increase the risk of stroke in atrial fibrillation patients: refining the $CHADS_2$ score. *Int J Cardiol* 2011;146:131−133.
17. Mansukhani MP, Calvin AD, Kolla BP, Brown RD Jr, Lipford MC, Somers VK, Caples SM. The association between atrial fibrillation and stroke in patients with obstructive sleep apnea: a population-based case-control study. *Sleep Med* 2013;14:243−246.
18. Hayakawa T, Terashima M, Kayukawa Y, Ohta T, Okada T. Changes in cerebral oxygenation and hemodynamics during obstructive sleep apneas. *Chest* 1996;109:916−921.
19. Valipour A, McGown AD, Makker H, O'Sullivan C, Spiro SG. Some factors affecting cerebral tissue saturation during obstructive sleep apnoea. *Eur Respir J* 2002;20:444−450.
20. Savransky V, Jun J, Li J, Nanayakkara A, Fonti S, Moser AB, Steele KE, Schweitzer MA, Patil SP, Bhanot S, Schwartz AR, Polotsky VY. Dyslipidemia and atherosclerosis induced by chronic intermittent hypoxia are attenuated by deficiency of stearoyl coenzyme A desaturase. *Circ Res* 2008;103:1173−1180.
21. Urbano F, Roux F, Schindler J, Mohsenin V. Impaired cerebral autoregulation in obstructive sleep apnea. *J Appl Physiol* 2008;10:1852−1857.
22. Caples SM, Somers VK, Phil D. Sleep disordered breathing and atrial fibrillation. *Prog Cardiovasc Dis* 2009;51:411−415.
23. Young T, Evans L, Finn L, Palta M. Estimation of the clinically diagnosed proportion of sleep apnea syndrome in middle-aged men and women. *Sleep* 1997;20:705−706.
24. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. *Am J Respir Crit Care Med* 2002;165:217−239.
25. Todd K, Mclntyre WF, Baranchuk A. Obstructive sleep apnea and atrial fibrillation: a review of literature. *Nat Sci Sleep* 2010;2:39−45.
26. Peker Y, Glantz H, Thunström E, Kallryd A, Herlitz J, Ejdebäck J. Rationale and design of the Randomized Intervention with CPAP in Coronary Artery Disease and Sleep Apnoea—RICCADSA trial. *Scand Cardiovasc J* 2009;43:24−31.
27. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of atrial fibrillation. *JAMA* 2001;285:2864−2870.
28. Hart RG, Pearce LA, Rothbart RM, McAnulty JH, Asinger RW, Halperin JL. Stroke with intermittent atrial fibrillation: incidence and predictors during aspirin therapy. Stroke Prevention in Atrial Fibrillation Investigators. *J Am Coll Cardiol* 2000;35:183−187.
29. The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. *N Engl J Med* 1990;323:1505−1511.
30. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch Intern Med* 1994;154:1449−1457.